REMARKS

Status of the Claims

Claims 1-26, 35-37, and 49-53 are in the application.

Claims 1-8, 10-20, 22-26, 35-37 and 49-53 were rejected.

By way of this amendment, claims 1, 8, 10, 12, 16, 19-21, 23-26 and 52 have been amended, claims 22, 35, 37 and 53 have been canceled and new claims 58-67 have been added.

Upon entry of this amendment, claims 1-8, 10-20, 23-26, 36, 49-52 and 58-67 will be pending.

Summary of the Amendment

Claim 1 has been amended to more clearly set forth the claimed subject matter. Reference to "cancer cells with a high rate of glycolysis" has been added to the preamble. The claim as presented earlier specifically recites the element of "cancer cells with a high rate of glycolysis". As amended, the claim is clearer. The scope of claim 1 remains the same as previously presented. Claim 1 is a Markush claim in which the two types of compounds, citrate lyase inhibitors on the one hand and tricarboxylate transporter inhibitors on the other hand, are presented as alternatives. Applicants have elected citrate lyase inhibitors, specifically citrate lyase, for initial examination.

Claim 8 has been amended to delete reference to language asserted to be indefinite.

Claim 10, which differs in scope from claim 1 in that claim 10 does not refer to tricarboxylate transporter inhibitors, has been amended to more clearly set forth the claimed subject matter. Reference to "cancer cells with a high rate of glycolysis" has been added to the preamble similar to the amendment to claim 1. Additionally, incorporating the limitation of claim 11, such language has been added as an element in the body of the claim. Claim 10 has also been amended to add the recitation of the step of identifying the cancer as a cancer comprising "cancer cells with a high rate of glycolysis".

Claim 11 has been deleted as redundant in view of the amendment of claim 10.

Claim 12 has been amended to update its dependency in view of the incorporation of the subject matter of claim 11 into claim 10.

Claim 16 has been amended to combine subject matter from claim 16 by adding the recitation of "cancer cells with a high rate of glycolysis" in the preamble. The step of identifying the cancer as a cancer comprising "cancer cells with a high rate of glycolysis" has been added to claim 16. Moreover, claim 16 has been amended to change it from a Markush claim in which citrate lyase inhibitors and tricarboxylate transporter inhibitors are presented as alternatives. As amended, claim 16 recites that both a citrate lyase inhibitor and a tricarboxylate transporter inhibitor are administered to the individual. The dosage limitation for the citrate lyase inhibitor has also been deleted from claim 16 in favor of new claim 67.

Claim 19-21, 25 and 26 have each been amended to delete language rendered unnecessary by the amendment of claim 16.

Claim 20 has also been amended to delete reference to language asserted to be indefinite.

Claim 22 has been canceled in view of the amended of claim 16.

Claims 35 and 37 have been canceled as being redundant with claim 19 in view of the amendment of claim 16.

Claim 52 has been amended to combine subject matter from claim 53 by adding the recitation of "cancer cells with a high rate of glycolysis" in the preamble. The step of identifying the cancer as a cancer comprising "cancer cells with a high rate of glycolysis" has been added to claim 52.

Claim 53 has been canceled in view of the amended of claim 52.

New claims 58-62 refer to different embodiments of the subject matter in claim 52. New claims 58-62 correspond to claims 2 and 12, claims 3 and 13, claim 7, claim 14 and claim 15, respectively.

New claims 63-66, which are dependent on the independent claims 52, 1, 10 and 16, respectively, refer to the cancer as being a glioma, the elected species.

New claim 67 refers to subject matter that was deleted from claim 16.

No new matter has been added.

Claim Rejection Under 35 U.S.C. § 112, second paragraph

Claims 8 and 20 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to point out what is included by the claim language.

Claims 8 and 20 have been amended to delete language that was the basis for the rejection. As amended claims 8 and 20 refer to specific embodiments of the invention.

Claims 8 and 20 are clear and definite and in compliance with the requirements of the second paragraph of 35 U.S.C. § 112. Applicants respectfully request that the rejection of claims 8 and 20 under 35 U.S.C. § 112, second paragraph, be withdrawn.

Claim Rejection Under 35 U.S.C. § 103(a)

Kuhajda et al.

Claims 1, 4-8, 10, 11, 14, 15 and 50-53 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Kuhajda et al. (U.S. Patent No. 5,759,837; hereinafter referred to as "Kuhajda").

Kuhajda discloses methods of treating carcinomas characterized by cells that overexpress fatty acid synthase (FAS), that are dependent on endogenously synthesized fatty acid and that express an antigen referred to as OA-519. According to Kuhajda, such carcinomas are highly virulent and susceptible to death by treatment with FAS inhibitors. Kuhajda also discloses methods of treating carcinomas characterized by cells that are dependent on endogenously synthesized fatty acid by inhibiting the fatty acid synthesis pathway (see for example column 9, lines 10-35) Kuhajda teaches treating cancer by inhibiting lipid synthesis and suggests that such inhibition can be accomplished by directly inhibiting FAS or by inhibiting other enzymes in lipid synthesis such as those enzymes which catalyze reactions to produce products used in lipid metabolism. Three such enzymes disclosed are acetyl-CoA carboxylase, malic enzyme, citrate lyase. Hydroxycitrate is disclosed among the list of inhibitors of citrate lyase and the other enzymes.

Applicants respectfully note that claim 1 as examined and claims 10, 16 and 52 as amended recite the step of:

> identifying said cancer as a cancer that comprises cancer cells that have a high rate of aerobic glycolysis[.]

Each of the pending claims is directly or indirectly dependent on one of claims 1, 10, 16 and 52. Kuhajda neither teaches nor suggests identifying the cancer as comprising cancer cells which have a high rate of glycolysis.

In the rejection of the claims, including claims 1, 4-8, 50, 51 and 53, which each include the step of determining if the cancer comprises cancer cells that have a high rate of aerobic glycolysis, the step of identifying the cancer as comprising cancer cells that have a high rate of aerobic glycolysis is misstated and dismissed. On page 8 of the Official Action, the Office indicates that the step of "identifying a patient with cancer" is implicitly taught in the prior art. Claim 1 as examined states expressly states:

> identifying said cancer as a cancer that comprises cancer cells that have a high rate of aerobic glycolysis[.]

This identification step is neither explicitly nor implicitly disclosed in Kuhajda. The rejection as applied to the subject matter in claims 1, 4-8, 50, 51 and 53 as examined (and in each pending claim upon entry of this amendment) is flawed in that a required step in the claim is not found in the cited art. The claimed invention is not prima facie obvious in view of Kuhajda. One skilled in the art would not take the affirmative step of determining if the cancer comprises cancer cells that have a high rate of aerobic glycolysis. Absent the teaching of the present invention, one skilled in the art would not deem it obvious to determine an individual's cancer comprises cancer cells that have a high rate of aerobic glycolysis and if so, administer a citrate lyase inhibitor.

It is unclear from the Official Action whether or not the Office is asserting that all cancers have a high rate of aerobic glycolysis. In fact, they do not. As noted in paragraph 24 of the published specification:

> The present invention arises from the observation that many human cancers display a high rate of aerobic glycolysis and that this high rate of aerobic glycolysis leads to increasing dependence of the cancer cells on certain metabolic enzymes that are not normally required for the survival of vegetative cells.

That is, the specification clearly states that many human cancers have this property. By extension then, the specification teaches that not all human cancers have this property. Attached

hereto are three published references which each reflect this point; all cancers do not have a high rate of aerobic glycolysis.

The rejection of the claims is also flawed in that the cancer cells that have a high rate of aerobic glycolysis referred to in the present application are deemed to be disclosed or obvious by Kuhajda which discloses treating cancer by inhibiting lipid metabolism through inhibition of enzymes in the pathway. In the paragraph bridging pages 8 and 9, the Office states:

> With respect to the term "*comprises cancer cells that have a high rate of aerobic glycolysis*" (claims 1, 11, and 53), it is the examiner's position that Kuhajda et al. provides a general teaching of cancers, including cancers mediated by FAS, such that one would reasonably expect cancers mediated by FAS to be comprised of cancer cells that have a high rate of aerobic glycolysis since Kuhajda et al. teach that pyruvate is involved in lipid metabolism and pyruvate is also known to be involved in glycolysis (col. 16, lines 9-25).

This basis for the rejection is without merit. No reference is provided supporting the assertion that one would reasonably expect cancers mediated by FAS to be comprised of cancer cells that have a high rate of aerobic glycolysis. The reasoning, that because both the FAS pathway and glycolysis involve pyruvate, treating cancer mediated by FAS necessarily treats cancer that has a high rate of aerobic glycolysis, is flawed. Glycolysis by necessity converts pyruvate to lactate to regenerate NAD from NADH. As a result the pyruvate produced during aerobic glycolysis is not available to be converted into lipid through mitochondrial metabolism. While pyruvate is involved in both pathways, the pyruvate from the glycolysis pathways is not involved in the lipid synthesis pathway and there is no scientific basis for concluding the presence of pyruvate in both pathways somehow makes the pathways themselves interrelated as suggested. Applicants respectfully urge that, if Applicants' understanding of the point raised in the Official Action is incorrect, that the point be clarified. The pathways are well known and nothing is provided to contradict what is well known.

Applicants note that the invention in Kuhajda is in some respects analogous to the claimed invention in that both inventions treat cancer by inhibiting a pathway and causing

disruption of cells by such inhibition. However, while Kuhajda disclosed inhibiting lipid synthesis, the present invention relates to inhibiting glycolysis in cancers with cells that have a high rate of aerobic glycolysis. These two pathways are distinct. Moreover, the instant invention specifically requires identifying the cancer as having c ells that have a high rate of aerobic glycolysis prior to administering the citrate lyase inhibitor.

In view of the differences between the claimed invention and the teachings in Kuhajda, one skilled in the art would not consider the claimed invention obvious in view of Kuhajda. Nothing in the disclosure of treating cancer by inhibiting enzymes involved in the lipid synthesis pathway would render obvious treating cancer identified as comprising cancer cells with a high rate of aerobic glycolysis by administering a citrate lyase inhibitor after such identification. The pending claims are not unpatentable over Kuhajda under 35 U.S.C. § 103(a). Applicants respectfully request that the rejection of the claims under 35 U.S.C. § 103(a) as being unpatentable over Kuhajda be withdrawn.

Kuhajda et al. and Schroder et al.

Claims 2, 3. 12 and 13 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Kuhajda et al. (U.S. Patent No. 5,759,837; hereinafter referred to as "Kuhajda") in view of Schroder et al. (Intl. J. Gynecol. Cancer 1999(9):117-122; hereinafter referred to as "Schroder").

Kuhajda is discussed above.

Schroder discloses the use of PET and ^{18}fluoro-deoxyglucose in the diagnosis of ovarian cancer.

It is asserted that it would have been obvious to one skilled in the art to identify an individual as having cancer using PET scanning and then treating them according the teachings of Kuhajda. Applicants respectfully disagree.

As stated above, the claims are not limited to the simple diagnosis of cancer but more specifically to the identification of cancer as being characterized by a high rate of aerobic glycolysis. Nothing in either Kuhajda or Schroder teach or suggest that cancer characterized by a

high rate of aerobic glycolysis is particularly susceptible to treatment involving the inhibition of citrate lysase.

As disclosed throughout the specification and shown in Example 2, citrate lysase inhibitors are effective therapeutics which selectively induce cell death in cancer characterized by a high rate of aerobic glycolysis. Applicants' have claimed a method which includes characterizing cancer by its level of glucose metabolism and treating those individuals identified as having a certain metabolic characteristic, i.e. a high rate of aerobic glycolysis. As shown in Example 2, citrate lysase inhibitors have very specific anticancer properties with respect to this subpopulation of cancer cells. Nothing in Kuhajda and Schroder teach or suggest to one skilled in the art that citrate lysase inhibitors would be particularly useful in treating cancers characterized by a high rate of aerobic glycolysis.

In view of the differences between the claimed invention and the teachings in Kuhajda and Schroder, one skilled in the art would not consider the claimed invention obvious. Nothing in the combination of references would render as obvious, the method of identifying a cancer as being characterized by a high rate of aerobic glycolysis and then, treating cancer identified as such by administering a citrate lyase inhibitor after such identification. The pending claims are not unpatentable under 35 U.S.C. § 103(a)over Kuhajda and Schroder. Applicants respectfully request that the rejection of the claims under 35 U.S.C. § 103(a) as being unpatentable over Kuhajda and Schroder be withdrawn.

Kuhajda et al. and Bru et al.

Claims 16-20, 22, 25, 26, 35-37 and 49 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Kuhajda et al. (U.S. Patent No. 5,759,837; hereinafter referred to as "Kuhajda") in view of Bru et al. (U.S. Patent No. 5,219,846; hereinafter referred to as "Bru")

Kuhajda is discussed above.

Bru discloses the use of compounds asserted to be tricarboxylate transport inhibitors to teat cancer.

It is asserted that it would have been obvious to one skilled in the art to combine the teachings of Kuhajda and Bru to produce the claimed invention.

As stated above, the claims have been amended to recite the step of identifying cancer as being characterized by a high rate of aerobic glycolysis. Nothing in either Kuhajda or Bru teach or suggest that cancer characterized by a high rate of aerobic glycolysis is particularly susceptible to treatment involving the inhibition of citrate lysase. Nothing in either Kuhajda or Bru teach or suggest determining if a cancer is characterized by a high rate of aerobic glycolysis prior to treatment.

As previously noted, throughout the specification and shown in Example 2, citrate lysase inhibitors are disclosed to by effective therapeutics which selectively induce cell death in cancer characterized by a high rate of aerobic glycolysis. The claimed a method include characterizing cancer by its level of glucose metabolism and treating those individuals identified as having a certain metabolic characteristic, i.e. a high rate of aerobic glycolysis. As shown in Example 2, citrate lysase inhibitors have very specific anticancer properties with respect to this subpopulation of cancer cells. Nothing in Kuhajda and Bru teach or suggest to one skilled in the art that citrate lysase inhibitors would be particularly useful in treating cancers characterized by a high rate of aerobic glycolysis.

In view of the differences between the claimed invention and the teachings in Kuhajda and Bru, one skilled in the art would not consider the claimed invention obvious. Nothing in the combination of references would render as obvious, the method of identifying a cancer as being characterized by a high rate of aerobic glycolysis and then, treating cancer identified as such by administering a citrate lyase inhibitor and a tricarboxylate transport inhibitor. The pending claims are not unpatentable under 35 U.S.C. § 103(a)over Kuhajda and Bru. Applicants respectfully request that the rejection of the claims under 35 U.S.C. § 103(a) as being unpatentable over Kuhajda and Bru be withdrawn.

Conclusion

Claims 1-8, 10-20, 23-26, 36, 49-52 and 58-67 are in condition for allowance. A notice of allowance is earnestly solicited. Applicants invite the Examiner to contact the undersigned at 610.640.7855 to clarify any unresolved issues raised by this response.

The Commissioner is hereby authorized to charge any deficiencies of fees and credit of any overpayments to Deposit Account No. 50-0436.

Respectfully submitted,

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